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REVIEW

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Placebo Effects in a Multiple Sclerosis Spasticity Enriched Clinical Trial with the Oromucosal Cannabinoid Spray (THC/CBD): Dimension and Possible Causes

Vincenzo Di Marzo[1] & Diego Centonze[2,3]

1 Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Naples, Italy
2 Department of Systems Medicine, Multiple Sclerosis Clinical and Research Center, Tor Vergata University, Rome, Italy
3 IRCCS Santa Lucia Foundation, Rome, Italy

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Correspondence
Dr. Diego Centonze, M.D., Ph.D., Department of Systems Medicine, Multiple Sclerosis Clinical and Research Center, Tor Vergata University, Via Montpellier 1, 00133 Rome, Italy.
Tel.: +39-6-7259-6010;
Fax: +39-6-7259-6006;
E-mail: centonze@uniroma2.it
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SUMMARY

Regulatory authorities admit clinical studies with an initial enrichment phase to select patients that respond to treatment before randomization (Enriched Design Studies; EDSs). The trial period aims to prevent long-term drug exposure risks in patients with limited chances of improvement while optimizing costs. In EDSs for symptom control therapies providing early improvements and without a wash-out period, it is difficult to show further improvements and thus large therapeutic gains versus placebo. Moreover, in trials with cannabinoids, the therapeutic gains can be further biased in the postenrichment randomized phase because of carryover and other effects. The aims of the present review article are to examine the placebo effects in the enrichment and postenrichment phases of an EDS with Δ^9-tetrahydrocannabinol and cannabidiol (THC/CBD) oromucosal spray in patients with multiple sclerosis (MS) spasticity and to discuss the possible causes of maintained efficacy after randomization in the placebo-allocated patients. The overall mean therapeutic gain of THC/CBD spray over placebo in resistant MS spasticity after 16 weeks can be estimated as a ~1.27-point improvement on the spasticity 0–10 Numerical Rating Scale (NRS; ~−20.1% of the baseline NRS score). We conclude that careful interpretation of the results of EDSs is required, especially when cannabinoid-based medications are being investigated.

Introduction

Placebo effects in trials of therapy for symptomatic management of chronic conditions are difficult to predict, and their resulting figures can vary broadly from those estimated when developing the study protocol. In a recent review of parallel-group neuropathic pain trials with similar design, the placebo effect ranged from 11% to 50% while the active-arm effects ranged from 20% to 60%, leading to a therapeutic gain (the difference between the efficacy score of the active medication group and the placebo group) ranging from 10% to 35% [1]. The assumption that the difference between the drug and the placebo groups only depends on the pharmacodynamic actions of the drug may, under certain circumstances, be mistaken [2] as the drug can also modulate the expectancy of treatment effects [3]. Enriched Design Studies (EDSs) are clinical studies in which a trial period for the test medication is included in the design; the participants are exposed to the active medication in a single-blind manner in an initial trial period phase and, if reaching a predefined initial response threshold after a predetermined follow-up period, are then randomized to continue with either placebo or active medication (double-blind) in the second phase. Nonearly responders discontinue treatment at the end of the trial period. EDSs appear not to bias the results of efficacy [4] but may result in achieving a smaller therapeutic gain in the placebo-controlled, randomized postenrichment period [5,6]. A washout period between phases might be considered, but practical and ethical reasons usually prevent this.

In symptomatic conditions such as spasticity (muscle tone increase causing rigidity, often associated with pain and spasms) [7], clinical trials for classic medications such as baclofen or tizanidine, have frequently shown difficulties in reaching statistically significant differences versus placebo [8,9]. A Δ^9-tetrahydrocannabinol and cannabidiol (THC/CBD) oromucosal spray (trade mark Sativex®; USAN name Nabiximols, GW Pharmaceuticals Ltd, Salisbury, UK) has been approved across the EU and in other countries for the treatment of moderate to severe spasticity in patients with multiple sclerosis (MS) resistant to oral treatments following positive risk/benefit evaluations from the clinical trials dossier with placebo-controlled studies [10]. THC/CBD oromucosal spray showed benefits where oral medications had failed, albeit only in one-third to half of the previous resistant patients, and was associated with adverse events such as somnolence or dizziness (mild to moderate, transient) and few serious nervous system events [5]. The largest pivotal study in the THC/CBD spray development plan, reviewed herein, was an EDS [5], which is a type of trial increasingly favored by the regulatory authorities [11] to avoid risks and to save time/resources in everyday clinical practice by discontinuing nonresponders early when no other predictors of response are available. The trial period is therefore requested in the medication label. In this study, initial responders after the 4-week trial phase with the active medicine (defined as achieving a 20% improvement in the spasticity 0–10 Numerical Rating Scale (NRS) score versus baseline [12]; 47% of the exposed sample) did not rapidly lose the initial benefit when switched randomly to placebo (n = 117) and still exhibited reduced spasticity after 12 weeks of placebo treatment, although statistically to a significantly lesser extent than the 124 patients that continued on THC/CBD spray. Three previous non-EDSs of THC/CBD spray for MS spasticity had shown a stronger, statistically significant separation between treatment and placebo both in their individual and pooled analyses [13–16]. In a different THC/CBD spray withdrawal study [17], 36 long-term responders to THC/CBD spray (mean exposure 3.6 years) were randomized to continue either with THC/CBD spray or with placebo: 55.5% of those assigned to the THC/CBD spray group were still on the medication after 4 weeks as opposed to 5.5% of those in the placebo group. This latter study shows a quick and strong separation between the active and placebo arms, contrary to what was seen in the reviewed EDS [5]. Additionally, the effectiveness of THC/CBD spray in daily practice in an observational large study conducted after medication approval (with about half of previously resistant patients with MS spasticity being maintained on treatment after 3 months) is aligned with the clinical trial findings on the effect of the drug [18].

Here, we examine the placebo effect in the non-EDS large clinical trials of THC/CBD spray in MS spasticity, attempting to estimate the weight of the placebo effect on the medication during the 4 weeks of the enrichment phase of the reviewed EDS trial. We also provide possible explanations about the placebo effect origin and examine why, when such an effect was evaluated only in the randomized, posttrial phase of a THC/CBD spray EDS [5], it seemingly occurred to a greater extent than that observed in the non-EDS double-blind, placebo-controlled parallel-group trials [13–15].

Methods

Estimating the Placebo Effect in the THC/CBD Spray EDS Initial Phase

To explain the placebo effect in the enriched phase of the THC/CBD spray EDS [5], we evaluated the placebo and active-arm effects seen in other THC/CBD spray MS spasticity studies, in which patients receiving placebo and active drug treatment were randomized from the start (detailed features of these randomized, placebo-controlled, parallel-group clinical trials are described elsewhere [13–15]). These trials were approved by the relevant Institutional Review Board or Ethics Committee in each of the applicable countries and were conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Firstly, the pooled analyses presented here use patient data collected during the three main standard parallel-group efficacy trials [13–15]. In two of the pooled trials [14,15], spasticity was the primary variable and all patients contributed data. In the third (smaller) trial [13], a compiled symptoms score was the main endpoint and spasticity was one of several primary MS symptoms assessed. Therefore, only the data from randomized patients with MS spasticity declared as their main symptom were used in this exercise, considering the spasticity scale their primary outcome measure. Further comparative design details for the three trials are given below (Table 1A–D).

To facilitate pooling of the data, the Visual Analogue Scale spasticity scale data used in the smaller trial [13] were converted from the 0–100 scale to a 0–10 scale using a simple linear transformation. In both scales, the end points used were the same with "0 = no problem from spasticity" and "10 = the worst problem I can imagine".

The 2010-approved summary of product characteristics for THC/CBD spray in MS spasticity states that twelve sprays is the maximum number allowed per day. The EDS mentioned above adhered to this limit. To mimic this population, the selected summaries of the pooled non-EDS studies used only those subsets of subjects who used no more than 12 sprays per day.

All presentations are based primarily on the intention-to-treat (ITT) population as reported in the individual study reports and publications. The primary analysis used data from the preplanned final outcome assessment at 6 weeks in two studies [13,14], and at 14 weeks in the other study [15]. However, data from week six in the latter study were also analyzed.

The data were analyzed using a general linear model in which the dependent variable was the change from baseline in spasticity NRS assessment as the preferred option to minimize biases. Fixed factors included in the model were study, treatment group (THC/CBD spray/placebo), and the treatment group by study interaction term. Baseline spasticity was included as a covariate. Homogeneity of variance was tested using the Brown and Forsythe's test [19]. The interaction term was dropped from the model if not statistically significant ($P > 0.10$). The adjusted means for each treatment group are provided together with the estimated difference between treatments, 95% confidence intervals (CI) for the difference, and corresponding P value.

An "initial responder" definition of "a patient who experiences a reduction in spasticity score of 20% or greater from baseline for

Table 1 Magnitude of placebo effect on spasticity assessment in individual studies and pooled data

Variable	Study	Study duration (Weeks), Sample (n)	Adjusted mean change from baseline		Therapeutic gain	95% Confidence intervals for therapeutic gain	*P* value
			THC/CBD spray (N)	Placebo (N)			
(A)							
Mean spasticity 0–10 NRS (ITT)	Study 1 Wade et al. [13]*	6, 160	−1.55 (20)	−0.12 (19)	1.43	0.10, 2.76	0.03
	Study 2 Collin et al. [14]	6, 189	−1.11 (120)	−0.59 (64)	0.52	−1.029, −0.004	0.048
	Study 3 Collin et al. [15]	14, 337	−1.05 (166)	−0.82 (169)	0.23	−0.59, 0.14	0.220
	Pooled data	–	−1.16 (306)	−0.75 (252)	0.41	0.12, 0.70	0.006
(B)							
Mean spasticity 0–10 NRS (PP)	Study 1 Wade et al. [13]*	6, 160	–	–	–	–	–
	Study 2 Collin et al. [14]	6, 189	−1.23 (99)	−0.50 (54)	0.73	−1.286, −0.178	0.010
	Study 3 Collin et al. [15]	14, 337	−1.30 (122)	−0.84 (143)	0.46	−0.88, −0.03	0.03
			Proportion of responders				
(C)							
Responders ≥30%	Study 1 Wade et al. [13]*	6, 160	45.0% (20)	15.8% (19)	29.2%	1.93, 56.49%	0.051
Spasticity 0–10 NRS (ITT)	Study 2 Collin et al. [14]	6, 189	40.0% (120)	21.9% (64)	18.1%	4.73, 31.52%	0.014
	Study 3 Collin et al. [15]	14, 337	30.7% (166)	24.9% (169)	5.9%	−3.71, 15.4%[a]	0.23
	Pooled Data	–	35.3% (306)	23.4% (252)	11.9%	4.40, 19.36%[a]	0.002
			Proportion of responders				
(D)							
Responders ≥30%	Study 1 Wade et al. [13]*	6, 160	–	–	–	–	–
Spasticity 0–10 NRS (PP)	Study 2 Collin et al. [14]	6, 189	42.4% (99)	18.5% (54)	23.9%	9.69, 38.12	0.004
	Study 3 Collin et al. [15]	14, 337	36% (122)	24% (143)	12%	0.816, 3.431	0.040

*Spasticity is measured using Modified Ashworth scale on a 1–100 Visual Analogue Scale. [a]Odd ratios.

the period of primary assessment" was derived from a study showing that an 18% change from baseline was the minimal clinically important difference [12]. The analysis was carried out using the Cochran–Mantel–Haenszel procedure adjusting for study. The odds ratio together with 95% CI is presented. Homogeneity of treatment effect was assessed using the Breslow–Day test and assessed for significance at the 10% level.

For all analyses, no imputation was made for subjects whose baseline and/or endpoint data were missing or who were excluded from the analyses. Only where subjects failed to complete the study period were study endpoints imputed using a last-observation-carried-forward approach.

As a comparator for the maintenance of efficacy in the placebo-allocated patients in the second phase of the THC/CBD spray EDS (randomized phase), the authors performed PubMed searches for other EDSs (MeSH terms: Enriched AND design AND placebo), and also for cannabinoid studies (MeSH terms: THC OR tetrahydrocannabinol AND clinical trial AND placebo).

Results

Review of Placebo Data in Different THC/CBD Spray Non-EDS Randomized Clinical Trials

After the pooling of data from the THC/CBD spray clinical trials with a placebo arm from the start (i.e., initial responders), the mean overall reduction in the MS spasticity NRS score reported in the patients randomized to placebo achieving a 20% or greater improvement after 4 weeks was −2.57 points. These patients comprised 32.4% of those that took up to 12 sprays/day (Table 2).

If we apply this −2.57 placebo improvement figure to the EDS screening visit NRS mean score (6.9), the score would be reduced to 4.33 (−37.25%), while 3.9 was seen in the THC/CBD spray-treated patients who were responders at the 20% level at 4 weeks (−43.5% vs. baseline, therapeutic gain at this time point 6.25%, that is, 0.43 points on the 0–10 scale).

The improvement seen over placebo in the second (randomized) phase of the EDS, a further 0.84 NRS mean score (THC/CBD spray group −0.04 points further improvement, placebo group +0.81 worsening, $P = 0.0002$), can be added to the hypothetical 0.43 points of the first 4 week improvement over placebo, to obtain an estimated overall therapeutic gain of 1.27 NRS scale points, that is, −20.14% from the initial score (Figure 1).

Table 2 Magnitude of placebo effect on spasticity assessment at week 4 (studies [13–15] pooled data), ITT population

Variable	Group	Placebo (N)
Spasticity 0–10 NRS	Limited to 12 sprays No spray limit	Adjusted mean change from baseline −0.75 (71) −0.73 (252)
Responders ≥20% Spasticity 0–10 NRS	Limited to 12 sprays No spray limit	Proportion 20% responders 32.4% (71) 31.0% (252)
Spasticity 0–10 NRS	Limited to 12 sprays No spray limit	Adjusted mean change from baseline for 20% responders −2.57 (22) −2.56 (75)

Discussion

Possible Reasons for the Retention of Efficacy in Patients Randomized to Placebo in the EDS Postenrichment Phase

Several possible reasons may contribute to the partial retention of efficacy in patients randomized to placebo in the second phase of the reviewed EDS [5]. The placebo effect in this 12-week phase consisted of the following: patients on placebo deteriorated "only" a mean of 0.81 points in their NRS spasticity score from an end-of-first-phase mean score of 3.9, thus reaching a 4.71 mean score, which is significantly lower than their 6.9 NRS baseline preenrichment score, although also significantly higher than the final 3.86 NRS score of the patients who continued taking THC/CBD spray. This effect: (1) is probably overestimated by the fact that, if a parallel placebo arm had been run, the placebo-subtracted, end-of-first-phase score might have been 4.33 and not 3.9 (see Results) and, hence, the final NRS score of patients taking placebo thereafter might have been 5.14, which is not that different from the baseline value of 6.9, but still significantly higher than the final mean score of 3.86 of the patients taking THC/CBD spray in the second phase, and (2) might be due to the potential synergy of two peculiarities of this study: (a) the use of an EDS, which can cause pharmacodynamic priming effects, particularly with a medication targeting the endocannabinoid system (see below), (b) the role of the endocannabinoid system in placebo effects in general.

(a) EDS-related Pharmacodynamic Priming Effects

Classical double-blind, placebo-controlled studies with different treatments and for different chronic symptomatic conditions have shown that the loss of response after discontinuation of the medication might be slow. A very good example of this is the pregabalin (Lyrica®; Pfizer, New York, NY, USA) trial in the management of fibromyalgia, which was established in a 14-week, double-blind, placebo-controlled, multicentre study (named F1) [20] and in a 6-month, randomized, withdrawal study (named F2) [21], in which it took more than 3 weeks to obtain similar placebo response rates in previous active medication responders.

Indeed, both active drug and placebo administration can produce in the patient either the expectation of ameliorating their symptoms or the generation of anxiety about the fact that their symptoms may not improve. Either the "rewarding" effect of symptom relief or the disappointing effect of lack of efficacy can have profound effects upon anatomical and neurochemical mechanisms controlling emotion and stress, which in turn strongly influence (and are influenced by) the endocannabinoid system [22,23]. Thus, any run-in phase including a treatment, be it placebo or active drug, may somehow influence the effect of the treatment in subsequent phases of the trial and might involve altered activity of the endocannabinoid system. If a trial involves a drug which targets, at least in part, such system, as does THC/CBD

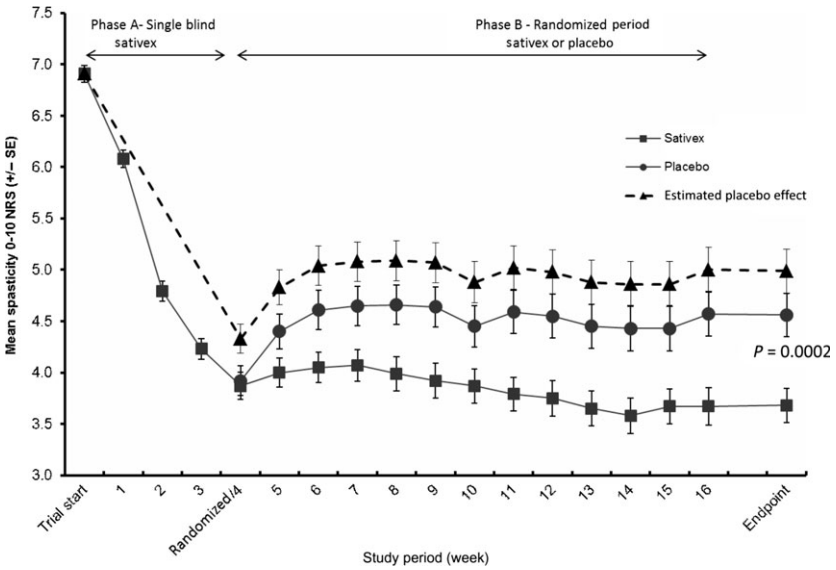

Figure 1 Mean spasticity 0–10 Numerical Rating Scale (NRS) scores for an enriched design study [5] and estimated placebo response from pooled data. The dashed line in Phase A is the calculated placebo effect, based on an analysis of pooled data from RCTs. The dashed line in Phase B represents the actual placebo response seen in Phase B of the Enriched Design Studies (EDS). This illustrates the estimated therapeutic gain that would have been observed if it was a conventional, nonenriched design study conducted in treatment responders.

spray, the priming effect of the initial phase might be even stronger. For example, one might envisage a long-term alteration of either endocannabinoid levels or the expression of cannabinoid receptors induced by the 4 weeks of the enrichment phase with THC/CBD spray in the EDS reviewed here [5], which would then influence both the effect of continuation of the treatment with the drug and its withdrawal.

No specific study has been carried out to investigate the effect of noncannabinoid therapeutic drugs on the endocannabinoid system in a clinical setting. However, (1) several drugs for affective disorders such as antipsychotics [24,25], antidepressants [26–28], and benzodiazepines [29] modify endocannabinoid levels or brain cannabinoid receptor expression and signaling in animal studies (see also [29] for review), (2) gene polymorphisms impacting on endocannabinoid levels and action influence the response to some drugs such as citalopram in humans [30], and (3) prolonged use of substances that act on neurochemical substrates of reward and emotion modify, in a long-lasting manner, endocannabinoid tone [31].

The first phase of successful active drug treatment may also cause priming effects in terms of changes in brain (cortical) plasticity due to readjustment to a "less-spastic condition." Spasticity and prolonged treatment with efficacious antispasticity drugs modify motor cortex synaptic plasticity and its role in the control of muscle contraction in a very long-lasting manner [32–34]. This alteration, although in principle occurring with all types of antispasticity treatments, may affect particularly those treatments targeting the endocannabinoid system given the major role of endocannabinoid retrograde signaling in plasticity. Induction of long-term potentiation (LTP)-like plasticity through repetitive or theta-burst transcranial magnetic stimulations of the primary motor cortex has long-lasting antispastic effects in patients with MS [35,36]. LTP induction is under the control of the endocannabinoid system and, indeed, oromucosal THC/CBD spray has been shown to favor LTP induction in the motor cortex of patients with MS [37]. Long-lasting adaptive changes in the motor cortex may thus explain, at least in part, the retention of efficacy of THC/CBD spray in patients later randomized to placebo.

THC (similarly to synthetic cannabinoid CB_1 and CB_2 receptor agonists) and CBD, the two active components of THC/CBD spray, both produce antiinflammatory and neuroprotective effects in animal models of MS [38]. Therefore, the possibility exists that a treatment as efficacious for spasticity as that observed after the first phase of the study may have also led to some long-lasting disease (MS) modification, which may also cause long-lasting symptom alleviation. The inflammatory milieu typical of MS brains causes loss of sensitivity of cannabinoid CB_1 receptors controlling synaptic transmission [39]. The potential antiinflammatory effects of THC/CBD spray treatment may have rescued CB_1 receptor expression and function in the run-in phase of the trial, thus providing symptomatic relief against spasticity even after the discontinuation of THC/CBD spray in the placebo arm. If this was the case, one would expect to have a different disease-modifying effect depending on the subset of MS (primary progressive, secondary progressive, or relapsing/remitting), which was not observed in the THC/CBD spray studies, although the disease inflammatory features might have been limited in the mid to advanced patients with MS enrolled. It would therefore be interesting to see which of the subsets of patients retained the effect of THC/CBD spray for longer and whether this retention can identify a subset for better response.

However, it must be emphasized that spasticity relief due to any hypothetical long-lasting, disease-modifying action of THC/CBD spray seen after only 4 weeks of run-in treatment in the EDS should have been seen also in a more prolonged treatment. Instead, in the THC/CBD spray MS spasticity double-blind, randomized, withdrawal study, a lower number of patients (n = 18 + 18) receiving long-term benefit from THC/CBD spray (up to 3.6 years) quickly lost the benefit when randomized to placebo, reaching statistical significance in the main parameter (time to treatment failure) [17].

(b) Role of the Endocannabinoid System in Placebo Effects: Do Placebo and THC/CBD Spray have Overlapping Mechanisms of Action?

The endocannabinoid system is emerging as a player in both non-opioid [35,36] and opioid [36] receptor-mediated, placebo-induced analgesia in humans. The expectation to receive relief from an aversive condition such as spasticity and spasms can be interpreted by the brain as a "reward", which is well known for activating the endocannabinoid system in a long-lasting manner [37]. As a consequence, placebo effects on aversive conditions are likely to be partly mediated by the endocannabinoid system and hence to have a mechanism of action which partly overlaps with that of THC/CBD spray. Thus, perhaps a much stronger separation than that observed in the second part of the EDS between THC/CBD spray and placebo should not have been expected. In fact, if the role of enhanced endocannabinoid levels and CB_1 receptor activity in determining the efficacy of placebo against spasticity are as strong as suggested for pain [40,41], the administration of placebo in the second phase of the EDS might have been almost equivalent to continued administration of THC/CBD spray, in which one of the two active ingredients (i.e., THC) is a CB_1 agonist.

A single nucleotide polymorphism (SNP) in the gene that encodes an important endocannabinoid-inactivating enzyme, fatty acid amide hydrolase, increases its sensitivity to proteolytic degradation, yet is associated with weaker placebo-induced analgesia [41]. This observation, although seemingly counterintuitive as the bearers of this SNP should have higher endocannabinoid levels and hence lower pain thresholds, was explained by the authors as possibly due to endocannabinoid-induced desensitization of CB_1 receptors [41]. This is in agreement with our hypothesis that placebo effects and medications that activate CB_1 receptors may have an overlapping mechanism of action. It would be interesting to see the frequency of this polymorphism in the 117 subjects that took placebo after randomization in the EDS, as it is possible that response to placebo and response to THC/CBD spray, or other treatments for MS spasticity, are determined by similar factors such as the availability and functional activity of CB_1 receptors. A genetic polymorphism of the *CNR1* gene associated with reduced CB_1 receptor expression was recently reported [42]. It would be interesting in future studies to test not only the clinical response to THC/CBD spray but also the response to placebo in patients carrying genetic variants associated with high or low levels of CB_1 receptor expression, as one would expect a similar high responsiveness to placebo when the CB_1 receptor is optimally expressed.

If the role of the endocannabinoid system in determining placebo effects may partly explain the small separation between placebo and active treatments in the randomized phase of the EDS reviewed here [5], one should expect to see a similar outcome also in other EDSs with endocannabinoid-based preparations. Indeed, in an EDS of the cannabinoid nabilone (a synthetic THC analog), Toth et al. [6] reported that peripheral neuropathic pain in patients assigned to placebo did not return to baseline values. After a 4-week enrichment period with nabilone, the patient population pain score improved by >2 points on the pain 0–10 NRS; at the end of the study (five further weeks follow-up), a worsening of only ~0.5 points was observed in the placebo arm versus an improvement of similar magnitude in the nabilone arm. The difference was statistically significant but the therapeutic gain in the randomized phase was limited to around 1 point on the pain 0–10 NRS. In a different therapeutic class, Furlan et al. [4] compared enriched and nonenriched design studies of opioids for chronic pain and found no difference in effect size when compared to placebo. Therefore, the calculation of therapeutic gain in EDSs with cannabinoid medications should be considered carefully.

Conclusions

The use of EDSs to identify patients who respond to a drug may lead to interpretation biases, as the overall therapeutic gain can easily be undervalued if the entire treatment period, including the trial period, is not considered.

The placebo effect in the treatment of symptomatic conditions should be evaluated carefully as the dimensions and duration can vary significantly from as short as 10% and up to as long as 50% depending on the condition under study, the study design, and the medication(s) tested [1].

In the prerandomized phase of the reviewed THC/CBD spray EDS, the mean therapeutic gain could be estimated from other THC/CBD spray studies and added to the therapeutic gain in the second phase, thus estimating an overall therapeutic gain of 20.1% over placebo.

The enhanced placebo effect size during the postenrichment phase in the reviewed study might be due to the role of the endocannabinoid system in the following: (1) the "priming effects" of the first phase of active drug treatment, which may contribute to the flattening of the NRS score worsening after allocation to placebo, and (2) placebo effects in general. Moreover, it is noteworthy that the EDS design is likely to allow early placebo responders to enter the randomization phase and that the probability of this appears greater in trials with cannabinoid medications, as similar neurobiological bases seem to underlie responses to cannabinoids and to placebo [40].

Further EDSs, including an external arm of untreated, similar patients and longer term follow-up periods, may offer a clearer explanation of the placebo effect in this setting. Furthermore, studies of possible predisposing genotypes and other factors would also help, although the multiple factors involved will render this task complex. Finally, functional neuroimaging and other measures of brain activity may help to clarify why the effects of placebo treatments differ between EDSs and randomized studies.

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Conflict of Interest

Vincenzo Di Marzo receives research funds and acts as a consultant for GW Pharmaceuticals Ltd, UK. Diego Centonze has received honoraria for speaking or consultation fees from Almirall, Spain and GW Pharmaceuticals Ltd, UK.

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